December 5, 2002

Dr. Anne P. LeHuray
Technical Contact
The American Chemistry Council
Rubber and Plastic Additives Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. LeHuray:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Hindered Phenols Category, posted on the ChemRTK HPV Challenge Program Web site on January 15, 2002. I commend The American Chemistry Council's Rubber and Plastic Additives Panel for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Hindered Phenols Category

SUMMARY OF EPA COMMENTS

The sponsor, the Rubber and Plastic Additives (RAPA) Panel Consortium of the American Chemistry Council, submitted a test plan and robust summaries to EPA for the Hindered Phenols category dated December 18, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 15, 2002. The category consists of eight sponsored phenols containing multiple aliphatic and/or aromatic substituent groups with at least one substituent positioned ortho to the phenolic hydroxyl group. The submitter has also included supporting data on three non-sponsored analogs.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. In general, the data provided by the submitter support the category with respect to the physicochemical, environmental fate and ecotoxicological properties of these substances; however, the other endpoints are less well supported. (a) The submitter did not discuss the phenolic hydroxyl group as a unifying feature. (b) The submitter did not address the reasons for the higher toxicity of the styrenated compounds or the implications for filling data gaps by extrapolation from existing data on non-styrenated compounds. (c) Available health effects data suggest there are significant differences among the category members that do not support the category as a whole.

2. Physicochemical Properties and Environmental Fate. (a) The submitter needs to provide measured boiling point data for additional category members. (b) The submitter needs to explain hydrolysis data for CAS No. 96-69-5. (c) The submitter needs to provide measured biodegradation data for CAS No. 7786-17-6. (d) The submitter needs to provide photodegradation studies for multiple chemicals representative of the category.

3. Health Effects. EPA believes that the available data cannot be extrapolated to the category members as a whole because some have multiple substituent groups that may impart significantly different toxicological properties. For the group of styrenated compounds, EPA recommends that the submitter conduct a combined reproductive/developmental toxicity screen on CAS No. 61788-44-1. EPA also considers that the triazinetrione (CAS No. 27676-62-6) does not fit into the category, and therefore evaluated it separately. A developmental toxicity study is necessary to address health effects for this chemical.

4. Ecological Effects. (a) For these endpoints EPA believes that the submitter needs to apportion the

chemicals into subclasses according to log Kow ranges and their resulting expected toxicity concerns. (b) Some acute fish, algal, and daphnia data submitted for three of the phenols that have log K_{OW} $ 7 are insufficient to address the endpoints because the concern in this case is for chronic effects. The submitter needs to provide missing critical acute data elements for other phenols, of log K_{OW} < 7, for which acute data are appropriate. (c) Where the log Kow suggests a chronic effects concern and no chronic data are available for that subclass, EPA suggests that the submitter needs to conduct a 21-day daphnia chronic test on the most hydrophobic member to satisfy the endpoint for this range of log Kow chemicals.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE HINDERED PHENOLS CATEGORY CHALLENGE SUBMISSION

Category Definition

The submitter proposed a category of eight substances defined as phenols containing multiple bulky aliphatic and/or aromatic substituent groups, with at least one substituent group positioned *ortho* to the phenolic hydroxy function.

The category consists of:

- Isobutylenated methylstyrenated phenol (CAS No. 68457-74-9)
- Styrenated phenol (CAS No. 61788-44-1)
- 4,4'-Thiobis(6-t-butyl-m-cresol) (CAS No. 96-69-5)
- 4,4'-Butylidenebis(6-t-butyl-m-cresol) (CAS No. 85-60-9)
- 4,4'-(1-Methylethylidene)bis(2-(1,1-dimethylethyl))phenol (CAS No. 79-96-9)
- 2,2'-Methylenebis(4-methyl-6-nonyl) phenol (CAS No. 7786-17-6)
- 4-Methylphenol, reaction products with dicyclopentadiene and isobutylene (CAS No. 68610-51-5)
- 1,3,5-tris(3,5-Di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (CAS No. 27676-62-6)

The submitter also provided supporting data on the following analogs:

- 2,6-Di-tert-butyl-p-cresol (CAS No. 128-37-0)
- 4-(Octadecanoxycarbonylethyl)-3,5-di-tert-butylphenol (CAS No. 2082-79-3)
- tetrakis(Methylene-3,5-di-tert-butyl-4-hydroxydihydrocinnamate)methane (CAS No. 6683-19-8)

The list on page 6/34 of the test plan has numerous errors, corrected above.

Category Justification

The submitter's category justification is based on structural features that are expected to impart similar physicochemical, environmental, and toxicological properties to the substances in the category. The common specific structural feature of the substances in this category is the presence of one or more *ortho*-

substituted phenol groups. In general, the data provided by the sponsor support the category with respect to the physicochemical, environmental fate and ecotoxicological properties of these substances; the health endpoints are less well supported.

Given the available information, the proposed category seems too diverse to be considered a single category for the purpose of extrapolating health effects. The variety of substituents adjacent to the hydroxyl group is considerable. While they all may be considered to hinder the hydroxyl group, they are sufficiently different to result in different toxicity in animal studies. For example, the two styrenated phenols appear to affect the thyroid, whereas the two tested substances that have two phenol rings bridged by a single atom appear to affect the liver. Data from the former class may not be appropriately extrapolated to the latter substances and vice versa. The remaining two chemicals, CAS No. 68610-51-5 with dicyclopentadiene substitution and CAS No. 27676-62-6 with a triazine ring, are unique molecules each of which differs from the rest in toxicological properties, and therefore should be considered outside the category and not used for data extrapolation purposes.

EPA disagrees with the submitter that ecotoxicity concerns for all category members are similar because their chemical properties are similar. The ranges of water solubility values and log Kow values are broad enough that the submitter should consider subcategories, because the concerns for acute and chronic toxicity will vary according to the way the category members are grouped, which in turn will depend on the relative amounts of various components in the mixtures.

EPA suggests that, along with available toxicity data, the submitter consider the following factors in determining possible subcategories.

– Phenolic chemicals with log Kow values < 7 are expected to show acute toxicity to aquatic organisms. (In reviewing the submission, EPA assumed X=1, Y=1, and n =2 to calculate log Kow values for CAS Nos. 68457-74-9 and 61788-44-1.)

– Phenolic chemicals in this category with log K_{ow} values between 7 and 9 (EPIWIN) raise a concern for chronic toxicity. Example: because a log Kow value of 9.08 was calculated for CAS No. 85-60-9, and acute toxicity was observed in algae, it can be considered a part of this subclass.

– For category members with Log K_{ow} values greater than 9 and low water solubility (e.g., CAS No. 68610-51-5), no toxicity is expected.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

EPA agrees that adequate data are available and no additional testing is necessary for melting point, vapor pressure, partition coefficient, and water solubility.

Melting Point. EPA identified two measured melting point values for CAS No. 79-96-9. The data from Handbook of Data on Organic Compounds and the Beilstein online database should be added to Test Plan Table 1.

Boiling Point. The submitter needs to test additional category members (CAS No. 85-60-9 and 27676-62-6); only two of the category members have measured values. The submitter states that calculated values will be used for the rest of the category. Technically, this agrees with OECD TG 103, which states that

measured values are not needed if the calculated boiling point is greater than 300°C. However, the measured and calculated values of CAS No. 61788-44-1 vary so drastically (230°C vs 422°C) that confidence in model results for these chemicals is low. Furthermore, measured values are preferred over calculated values as input parameters of models (such as fugacity) since they reduce the level of uncertainty. The submitter needs to provide measured boiling points for two additional compounds representing variations in structure.

Vapor Pressure. The vapor pressure value for CAS No. 68457-74-9 in Table 1 of the Test Plan needs to be corrected to read 1.8×10^{-5}.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Photodegradation. The submitter needs to provide photodegradation studies for multiple chemicals representative of the category (CAS Nos. 61788-44-1, 85-60-9, and 27676-62-6). Calculated values are provided for all category members. Both a measured and a calculated value are provided for CAS No. 128-37-0 and they vary substantially (75% after 8 days versus $t_{1/2}$ = 17 hours). Therefore, the photodegradation rates of compounds in this category may be overestimated and additional measured values need to be provided.

Stability in water. The test plan indicates that CAS No. 96-69-5, which apparently lacks a hydrolyzable functional group, undergoes slow degradation. The submitter needs to discuss the possible reasons–photodegradation? oxidation?–that might account for the loss of starting material, whether they are unique to this substance, and whether another study needs to be done to clarify the result.

Biodegradation. The submitter needs to provide measured data for CAS No. 7786-17-6. The data for the compounds in this category consistently show no or low biodegradability. However, CAS No. 7786-17-6 consists of linear alkyl chains and phenyl groups, both of which are biodegradable, and may be the most biodegradable category member..

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

All SIDS-level endpoints have been addressed for CAS No. 68610-51-5 for the purposes of the HPV Challenge program.

No SIDS-level health effects data were submitted for two category members (CAS Nos. 79-96-9 and 7786-17-6). Data submitted for two non-sponsored compounds (CAS Nos. 2082-79-3 and 6683-19-8) could not be evaluated because all robust summaries were inadequate. The submitter did not propose additional testing and did not explain the strategy for extrapolating from available data to the compounds with data gaps. EPA believes that it is inappropriate to extrapolate data from styrenated category members to non-styrenated category members or vice versa. A read-across strategy can be justified for the two styrenated compounds (CAS Nos. 68457-74-9 and 61788-44-1) and for the four substances that have two phenol rings bridged by a single atom (CAS Nos. 96-69-5, 85-60-9, 79-96-9, and 7786-17-6) as two separate subcategories. The remaining two category chemicals (CAS Nos. 68610-51-5 and 27676-62-6) could be considered as individual chemicals.

EPA recommends that the submitter conduct a combined reproductive/ developmental toxicity screening test (OECD GL 421) on CAS No. 61788-44-1 to address these endpoints for the styrenated compounds. In addition, a developmental toxicity study (OECD GL 414) is necessary for the triazine CAS No. 27676-62-6

to address the endpoint for that individual chemical. Available data for the two chemicals containing the bridged phenol group could be extrapolated to the other two chemicals in this group of four chemicals that have data gaps. The submitter needs to address deficiencies in several robust summaries.

Ecological Effects (fish, invertebrates, and algae)

The submitter needs to provide the typical values of X, Y, and N (in generic structures, test plan) where applicable for CAS Nos. 61788-44-1 and 68457-74-9 to determine appropriate log Kow ranges.

The submitted fish, algal, and daphnia data (CAS Nos. 61788-44-1, 68457-74-9, and the analog 128-37-0) were not adequate because the data did not provide a definitive value at the water solubility limit. The submitter needs to satisfy all three endpoints for one of these chemicals.

For CAS Nos. 96-69-5 and 85-60-9 (acute toxicity data for fish, daphnia and algae), EPA reserves judgment on data adequacy of some studies pending submission of critical missing data elements for these chemicals.

The calculated log Kows for CAS Nos. 7786-17-6, 2082-79-3, and 27676-62-6 are >13, which makes the acute data submitted questionable because no toxicity is likely at the chemicals' water solubility limit.

In Table 3 of the Test Plan, an EC50 value of 0.42 was reported, while in the robust summary a value of >0.42 was reported. The submitter needs to resolve this discrepancy.

Specific Comments on the Robust Summaries

Physicochemical Properties and Environmental Fate:

General: Citations and measured/calculated methods need to be added to the IUCLID data set for a number of chemical and environmental fate studies.

Melting Point. During an independent review, two measured melting point values were found for CAS No. 79-96-9. The data from Handbook of Data on Organic Compounds and the Beilstein online database should be added to the IUCLID data set.

Vapor Pressure. The vapor pressure reported in the IUCLID data set for CAS No. 7786-17-6 needs to be corrected by the submitter to read $0.8332648 \times 10^{-10}$ hPa.

Fugacity. The input values used in the fugacity calculations for all compounds need to be added to the robust summaries.

Health Effects

The health effects robust summaries were adequately detailed (requiring only minor additions) for only one category member, the triazinetrione. For the remaining compounds, one or more summaries did not include sufficient information to evaluate the study.

A common deficiency was the failure to identify the test material. The following methods of identification were inadequate: (a) referring to dossier section 1.1-1.4 when those sections were blank or nonexistent

(e.g., all summaries for CAS No. 68457-74-9), (b) giving only a physical description of the material (e.g., 'amber liquid' for CAS No. 61788-44-1 or 'white powder' for CAS Nos. 96-69-5 and 85-60-9), (c) using acronyms or trade names not defined in the summary or in dossier section 1.2 (e.g., Wingstay C for CAS No. 68457-74-9, TBBC or Santowhite crystals for CAS No. 96-69-5, Santowhite powder for CAS No. 85-60-9), and (d) indicating 'other TS, purity n%' (for the supporting compound CAS No. 128-37-0).

Acute Toxicity

Styrenated phenol. The robust summary for a GLP/OECD guideline acute oral toxicity study did not identify the test material or describe study design.

4,4'-Butylidenebis(6-tert-butyl-m-cresol). Omissions in the robust summary included: group size, length of observation period (oral), duration of exposure (dermal), body weight effects (oral), and the incidence of toxic effects by dose and sex.

1,3,5-tris(3,5-Di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione. Robust summaries did not include the purity of the test material and gross necropsy findings (oral).

Repeated-Dose Toxicity

Styrenated phenol. The robust summary for a 12-week feeding study in rats did not report purity of the test substance, the group size and experimental details.

4,4'-Thiobis(6-t-butyl-m-cresol). Robust summaries for subchronic and chronic NTP feeding studies in rats and mice used an undefined acronym (TBBC) to identify the test material. Omissions included results for mortality, body weight effects, and other effects by sex.

4,4'-Butylidenebis(6-tert-butyl-m-cresol). Robust summaries for 4-week and 90-day feeding studies in rats used an undefined trade name; 'Santowhite powder'. The summary for the 4-week study incorrectly listed the NOAEL as <1000 ppm rather than 'none;' the NOAEL refers to an 'observed' (i.e., tested) dose. In the robust summary for the 90-day study, microscopic changes seen in liver and lymph nodes need to be specified.

1,3,5-tris(3,5-Di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione. Robust summaries for three adequate 90-day feeding studies were complete except for the purity of the test material. The robust summary for a GLP/OECD-compliant subchronic study rats mis-stated the OECD guideline as 407 (28-day study) rather than 408 (90-day study). Summaries for non-GLP 90-day rat and dog studies mistakenly characterized them as 'subacute' rather than 'subchronic' studies.

Genetic Toxicity

Isobutylenated methylstyrenated phenol. Robust summaries omitted the standard name and purity of the test material. The summary of a guideline-like bacterial gene mutation assay, in addition, omitted the names of the positive control compounds.

Styrenated phenol. Robust summaries for negative gene mutation assays in bacteria and yeast omitted the compound name and experimental details. A robust summary for a non-guideline negative bacterial mutation assay was inadequate because it did not provide sufficient experimental details to evaluate the study.

4,4'-Thiobis(6-t-butyl-m-cresol). The robust summaries identified the compound by physical characteristics or undefined trade name; 'Santowhite crystals'.The robust summary of gene mutation assay in bacteria omitted the positive controls and source of the metabolic activation system. The summary of a gene mutation assay in yeast omitted experimental details (positive controls, etc.). The summary of an adequate GLP/OECD guideline-like chromosomal aberration assay in gavaged rats did not report the number of metaphases examined or the positive/negative controls.

4,4'-Butylidenebis(6-tert-butyl-m-cresol). Robust summaries for genotoxicity studies used an undefined trade name,'Santowhite powder.' Summaries for gene mutation assays in bacteria and yeast and unscheduled DNA synthesis in rat hepatocytes omitted critical details (especially cytotoxic concentration and positive controls). A robust summary for the chromosomal aberration study omitted details, such as the names of the positive controls, the solvent, duration of exposure, and number of cells that were analyzed.

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene. Robust summaries for three GLP-compliant *in vitro* studies (for mutation in bacteria and mammalian cells and for chromosomal aberration) and a non-GLP study of DNA damage and repair in bacteria omitted critical details needed to evaluate the studies: e.g. cytotoxic concentration, positive controls. The summary for the gene mutation assay in mammalian cells did not specify the concentration levels (tested and cytotoxic) and used discordant units in the concentration field and method field: ug/L and ug/mL. The summary implies that all concentrations were cytotoxic, which would invalidate the assay.

1,3,5-tris(3,5-Di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione. Summaries for *in vitro* studies of gene mutation and chromosomal aberration in mammalian cells and gene mutation in bacteria

omitted the cytotoxic concentrations and the source of the metabolic activation system; the latter also omitted the purity of the test material.

Reproductive Toxicity

4,4'-Thiobis(6-t-butyl-m-cresol). The robust summary did not report histopathology in reproductive organs in the NTP chronic rat feeding study. A reproductive screening assay was briefly described in dossier section 5.1 "Other Relevant Information, page 26/30; did not describe the study design.

4,4'-Butylidenebis(6-tert-butyl-m-cresol). The robust summary was adequate except for using an undefined trade name; 'Santowhite powder.'

1,3,5-tris(3,5-Di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione. There was no separate robust summary for reproductive toxicity endpoint; and no effects were noted in any reproductive organ in the 90-day guideline rat feeding study. The submitter needs to prepare a robust summary for reproductive toxicity endpoint and include it in that section of the document. A robust summary for the 24-month feeding bioassay described a two generation assay conducted on the same exposed rats from the bioassay; however, because of the low dietary concentration tested (100 ppm), this assay was considered inadequate.

Developmental Toxicity

4,4'-Thiobis(6-t-butyl-m-cresol). The robust summary for a study in rabbits omitted the following details: purity of test compound, endpoints examined, time of termination. It did not report the size of maternal body weight effect, which is needed to adequately identify the NOAEL/LOAEL values.

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene phenol. The robust summary for a GLP/OECD guideline study did not report the magnitude of the significant liver weight changes compared to controls and did not accurately identify the NOAEL/LOAEL values.

Ecotoxicity Studies

CAS No. 96-69-5: *Fish.* For the key study the submitter needs to provide water hardness, water temperature, chemical purity, pH, DO, identify carrier if used and concentration amount, number of test concentrations, and number of replicates per test.

Invertebrates. Missing critical data elements are water hardness, water temperature, pH, DO, number of test concentrations, and number of replicates per test.

Algae. Missing critical data elements are water hardness, water temperature, pH, DO, number of test concentrations.

CAS No. 85-60-9: *Invertebrate*. Missing critical data elements are water hardness, water temperature, pH, DO, number of test concentrations, and number of replicates per test.

Follow-up Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.